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## Childhood differentiated thyroid carcinoma: clinical course and late effects of treatment

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# CHAPTER I

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## General introduction



## The thyroid gland

The thyroid is an endocrine gland, located ventrally from the trachea. The gland consists of two lobes that are connected through the isthmus. The thyroid is composed of follicles, follicular cells, and parafollicular cells (also called C cells) (1). The follicular cells produce thyroxine (T<sub>4</sub>, thyroid hormone) and triiodothyronine (T<sub>3</sub>), which are composed of iodine and thyroglobulin (Tg, a precursor protein from the thyroid). T<sub>4</sub> is the sole product of the thyroid gland, whereas T<sub>3</sub> is produced in the thyroid and peripheral organs by deiodination of T<sub>4</sub>. Thyroid hormones are involved in a wide range of mechanisms within the body, and affect basal metabolic activity, growth, and neural development (2). Calcitonin, a hormone produced by the C cells and this hormone decreases the blood calcium concentration (3). The hypothalamic-pituitary-thyroid axis regulates the synthesis of the thyroid hormones. The hypothalamus releases thyrotropin-releasing hormone (TRH), causing the anterior pituitary gland to secrete thyroid-stimulating hormone (TSH). This results in thyroid hormone synthesis and secretion. T<sub>3</sub> and T<sub>4</sub> subsequently provide negative feedback to the hypothalamus and the pituitary gland (2).

## Thyroid cancer and differentiated thyroid cancer

Thyroid cancer ensues when cells of the thyroid gland reproduce uncontrollably and develop the potential to spread (metastasize). Histologically, the most common subtype of thyroid cancer is (well-)differentiated thyroid cancer (DTC, which includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC)). DTC accounts for 90% of all thyroid cancers (4, 5). Differentiated cancers derive from the follicular cells. DTC can occur at all ages, but its peak incidence is from the 3<sup>rd</sup> to 5<sup>th</sup> life decades (4). Poorly differentiated thyroid cancers, such as medullary thyroid cancer (MTC, arising from C cells) and anaplastic thyroid cancer (ATC, arising from the follicular epithelium) are less common (5, 6).

## Differentiated thyroid cancer in children

DTC in children (diagnosed before the age of 19 years) is rare, but incidence rates are increasing (7). Age-adjusted incidence rates of childhood DTC are 0.6 to 11.0 per 100,000, varying between age group and country of origin (7-9). Most children diagnosed with DTC are post-pubertal. Up to puberty, the incidence of DTC in boys and girls is similar, but from puberty onwards most patients are female (6), making female sex the most important risk factor for DTC. The explanation for this sex-dependent diagnosis probably lies within the proliferative effect of estrogen on thyroid cells, but the exact mechanism is not completely understood (10-12). The emergence of thyroid cancer cannot always be explained, but known risk factors for developing childhood thyroid cancer are exposure to radiation, iodine deficiency, a positive family history for DTC, gene rearrangements, or a thyroid cancer syndrome (13-15).

## **Symptoms of childhood differentiated thyroid cancer**

Children most often present with an asymptomatic solitary thyroid nodule or neck mass. Compressive symptoms, such as hoarseness, dysphagia, dyspnea, or experiencing a choking sensation are less common (16-18).

## **Diagnosis and treatment of childhood differentiated thyroid cancer**

Up to now, three official guidelines for the management of DTC in children have been published (19-21). Clinical evaluation, ultrasonography (US), and fine needle aspiration (FNA) are used to determine the origin of the thyroid nodule or neck mass (19). FNA can be makes it possible to obtain cells of the thyroid nodule and/or suspicious lymph node. The FNA of the thyroid nodule can then be evaluated according to the pathologic Bethesda System for Reporting Thyroid Cytopathology (22). Six different Bethesda diagnostic categories determine the follow-up measures, which range from clinical follow-up to surgical intervention (19, 22). When FNA indicates a strong possibility of malignant cells, treatment in children generally consists of a total thyroidectomy. Depending on the presence and the site of metastases, a central or (bi)lateral lymph node dissection can be performed (19). Children are postoperatively staged by means of the tumor-node-metastasis (TNM) classification (23, 24) and corresponding risk level of the disease (19), which determine the consecutive (intensity of the) treatment. After surgery, radioactive iodine ( $^{131}\text{I}$ ) can be administered. When administered in a high dose, the beta radiation of this radioisotope of iodine destroys thyroid cells (25), and may decrease the risk of recurrence of the disease (17, 26, 27). Although the precise role of  $^{131}\text{I}$  during treatment of low risk DTC has not yet been defined, the additional value of its administration in children with advanced disease is more established (27, 28). Subsequently, thyroid hormone supplementation with levothyroxine compensates the lack of thyroid hormone resulting from the thyroidectomy, but is also used to induce a certain level of TSH suppression (TSH suppression therapy). The aim of TSH suppression therapy is to suppress the growth-promoting effect of TSH on the thyroid cells, thereby preventing the (re)growth of malignant cells (29, 30). In high risk patients, a more intensive TSH suppression is advised. Recommendations are based on findings in adults, since no studies have as yet focused solely on evaluating children (19). Follow-up of the disease consists of clinical evaluation and neck palpation, US, and measuring of Tg during the thyroid hormone suppletion. Tg serves as a marker for residual or recurrent disease (19).

## **Outcome after treatment of childhood differentiated thyroid cancer**

Subsequent to treatment, survival rates of childhood DTC are up to 99% after 30 years of follow-up (6, 31). Although survival in children is excellent, a relatively high percentage (10 to 30%) of the children develops *recurrent disease*, occurring even decades after diagnosis (30, 32-34). Moreover, after treatment some patients still have

evidence of disease, which is called *persistent disease*. Recurrent or persistent disease occurs more frequently in patients with advanced disease upon diagnosis (35, 36).

Differentiated thyroid cancer in children and adults

In the past, DTC was presumed to be similar in children and adults. However, more advanced knowledge indicates great differences between DTC in children and adults.

Upon diagnosis, children present with more advanced and aggressive disease than do adults. Paradoxically, children have better overall survival rates in children than adults, but also more frequent persistent disease and recurrences (16-18, 31, 32, 34, 37-43). In childhood, the mutational landscape of DTC differs from that of adults (44-54). Table 1 presents an overview an overview of differences between DTC diagnosed during childhood and adulthood.

To date, however, no clear explanation can account for these differences between adult and childhood DTC. Although genetic alterations may play a role, studies are not conclusive. A higher expression of the sodium iodine symporter (NIS, essential in the uptake of iodine) in children may also help to explain their better responsiveness to <sup>131</sup>I administrations, but ultimately the origin of the difference between adult and childhood DTC is probably multifactorial.

Adverse effects after childhood cancer

Unfortunately, *survivors* of (childhood) cancer experience unwanted effects of the (treatment of the) cancer. These side effects are being increasingly recognized, as recent decades have seen an increase in the overall survival rate of childhood cancer (60). Side effects can occur during treatment, but may sometimes become manifest only years later. These *late effects* can be physical, mental, and/or psychosocial, such as cognitive impairment, fertility problems, diagnosis of a secondary malignancy,

Table 1. Differences between DTC diagnosed during childhood and adulthood

	Childhood DTC	Adult DTC
Malignant origin of thyroid nodules <sup>(16, 18, 39, 40)</sup>	19 to 26%	12 to 14%
Incidence of lymph node metastases <sup>(17, 31, 34, 41-43, 55)</sup>	40 to 90%	15 to 50%
Incidence of distant metastases <sup>(17, 56, 57)</sup>	20 to 30%	2 to 20%
Most prevalent mutational alteration <sup>(44-54)</sup>	RET fusion	BRAF V600E mutation
Recurrence rate <sup>(32, 34, 58)</sup>	Up to 32%	5%
Rate of persistent disease <sup>(32, 36, 58, 59)</sup>	5 to 33%	2 to 3%
10-year survival rate <sup>(17, 32, 37, 38)</sup>	95 to 100%	85 to 91%

Abbreviations: DTC, differentiated thyroid carcinoma; RET, rearranged during transfection; BRAF, v-raf murine sarcoma viral oncogene homolog B.

I and fatigue (61). Depending on the type of late effect, treatment or support can be offered, but not all effects can be prevented or resolved.

### **Adverse and late effects after childhood differentiated thyroid cancer**

Because the majority of childhood DTC patients will survive their disease, it is important to evaluate late effects in these survivors. However, in contrast to the knowledge of late effects in many other childhood malignancies, little is known about possible adverse effects of childhood DTC.

During treatment of DTC, surgical complications like surgical site infection, parathyroid damage (causing hypocalcaemia) and recurrent laryngeal nerve injury (causing hoarseness or loss of voice) can occur (62, 63). In addition, short-term side effects of  $^{131}\text{I}$  administration are radiation thyroiditis, nausea, vomiting, sialadenitis, gastro-intestinal symptoms, and bone-marrow suppression. In the long-term, administration of  $^{131}\text{I}$  for adult DTC is associated with salivary dysfunction or sialadenitis, pulmonary fibrosis, secondary malignancies, and gonadal damage in both men and women (causing fertility problems) (32, 64-69). Other long-term effects possibly induced by TSH suppression therapy are cardiovascular deterioration and loss of bone mineral density (also influenced by hypoparathyroidism) (29, 70-74). Moreover, general well-being or quality of life (QoL) can be affected by the diagnosis and the treatment of DTC (75-78).

Some studies have been performed in survivors of childhood DTC, but current knowledge is based mainly on late effects of DTC on adults. Because of the differences between childhood and adult DTC, as shown above, late effects may also differ. However, specific knowledge of the late effects of treatment for DTC during childhood is limited because of the scarcity of studies, the small number of patients evaluated, the lack of clear study definitions, or the poor quality of study designs.

### **Aims and outline of this thesis**

The aim of the current thesis is to evaluate the clinical course and late effects of childhood DTC. The results will ultimately benefit newly diagnosed patients, patients previously treated for DTC, caregivers, and treating physicians.

A multicenter, cross-sectional study was conducted in the Netherlands. Patients diagnosed with DTC before the age of 19 years between 1970 and 2013 were included. **Chapter 2** consists of an overview of the disease, treatment, outcomes, and follow-up characteristics of these patients. A minority of patients had distant metastases (DM). **Chapter 3** specifically evaluates the clinical course of DTC in a large cohort of childhood DTC patients diagnosed with DM. This study was performed at the University of Texas MD Anderson Cancer Center in the United States.

Long-term treatment effects of  $^{131}\text{I}$  after childhood DTC in the Netherlands are evaluated in the subsequent chapters. Female fertility after treatment is studied in

**Chapter 4**, where we evaluate reproductive characteristics in female survivors of childhood DTC, combined with levels of Anti-Müllerian hormone (AMH, a marker of ovarian reserve). Because the minority of childhood DTC patients is male, to attain a substantial and representative group of survivors, **Chapter 5** includes a study of male fertility after treatment in survivors of *adult* DTC. Male fertility was evaluated by performing semen analyses, and assessing reproductive hormones and reproductive characteristics. Adverse effects of long-term TSH suppression therapy are evaluated in **Chapter 6**, including effects on cardiac function in survivors of childhood DTC. The first evaluation of these patients, performed five years after their childhood DTC diagnosis, showed that 21% of the survivors had asymptomatic diastolic dysfunction (79). **Chapter 6** includes a re-evaluation of patients after a total follow-up period of 10 years to assess the course of their cardiac function. In **Chapter 7**, long-term thyroid cancer-specific QoL, health-related QoL, fatigue, and anxiety and depression are evaluated in survivors who were at least 5 years in follow-up after diagnosis. Because childhood cancer has been known to disrupt the course of life, **Chapter 8** evaluates psychosocial developmental milestones in childhood DTC survivors. **Chapter 9** contains the summary and general discussion of this thesis, and suggests its implications.



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